THE DICK TEST AND ACTIVE IMMUNIZATION WITH SCARLET FEVER STREPTOCOCCUS TOXIN

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AN IMPORTANT step in the final control of scarlet fever has been the recent work of the Dicks,[1] who definitely identified the hemolytic streptococcus associated with scarlet fever as the causative agent of the disease. They were able to produce experimental scarlet fever in human beings by planting upon the naso-pharyngeal mucous membrane of several volunteers a culture of the hemolytic streptococcus, which was obtained from the infected finger of a nurse taking care of cases of scarlet fever.

Their work and that of different investigators who claimed that the specific hemolytic streptococcus of scarlet fever formed a single agglutinative group, turned the attention of the medical profession once more toward this organism as the primary cause of scarlet fever. Among these observers may be mentioned Gordon,[2] Bliss,[3] Tunicliff,[4] and Dochez.[5] Williams of the Research Laboratory and the Dicks,[6] on the other hand, found that the different scarlet fever strains fell into different agglutinative groups.

With the identification of certain strains of the hemolytic streptococcus as the specific agent of scarlet fever, the Dicks continued their investigations and obtained a soluble toxic filtrate[7] from cultures of this organism, which gave positive skin reactions in early cases of scarlet fever and negative reactions in convalescence. Positive and negative reactions were also observed in normal individuals.

Zingher[8, 9, 10, 11] has confirmed and extended the observations of the Dicks on the skin test. Branch and Edwards[12] also confirmed the results of the Dicks. With the toxin the Dicks[13] have succeeded in immunizing actively a number of nurses. Zingher[10, 11] injected with gradually increasing doses of the toxin the positive reactors in a number of schools and institutions.

An antitoxic serum has also been produced by the Dicks[14] by injecting the toxin into horses. Dochez[15] a few months earlier obtained an antitoxic serum by a different method. He first injected a small amount of liquefied agar into the subcutaneous cellular tissue of the neck of a horse, and into the center of the agar nodule formed after its solidification he inserted the sedimented bacterial mass from a broth culture of the scarlatinal streptococcus. The bacteria were thus protected from the phagocytes, while the toxin according to Dochez could pass through the agar into the lymph spaces and cellular tissues of the animal and stimulate the production of antitoxin. A sloughing ulcer is formed at the site where the agar and bacteria have been injected. Very good therapeutic results have been claimed for the Dochez serum by Blake, Trask and Lynch.[16] At the Willard Parker Hospital the Dochez serum has given encouraging results, but not so striking as those reported by Blake and his associates.

MODERN CONCEPTION OF SCARLET FEVER

The absence of immunity after various infections with the hemolytic streptococcus has always been a strong point against accepting this organism as the specific etiological agent of scarlet fever. With the separation and identification of a toxin produced by the scarlatinal streptococcus

our conception of scarlet fever and the immunity following it have undergone a considerable change. We now consider the disease a local infection of the mucous membrane of the naso-pharynx in which a soluble toxin is produced. This is absorbed into the system of the patient, where it gives rise to the rash and other constitutional symptoms.

The disease thus resembles to a certain extent diphtheria. It differs, however, from diphtheria in that the toxin stimulates the production of an antitoxic immunity in nearly all patients and in the tendency of the hemolytic streptococcus to invade the body and produce gland, ear and joint infections. The immunity, therefore, to scarlet fever is chiefly *antitoxic* and not antibacterial, since patients who have recovered from scarlet fever either recently or in previous years may develop infections with the specific scarlatinal organism. These reinfections are not associated, however, with the characteristic clinical criteria of scarlet fever, a rash followed by desquamation. Similar infections without a rash may also occur in those who are "naturally" antitoxically immune to clinical scarlet fever and give a negative Dick reaction.

THE DICK TEST

The Dick test in relation to scarlet fever closely resembles the Schick test in relation to diphtheria. It consists of the intradermal injection of 0.1-0.2 c.c. of a dilution of the soluble toxic filtrate obtained from a culture of the specific hemolytic streptococcus. The toxin is made by growing the streptococcus for five to six days in broth containing five per cent defibrinated or citrated horse blood. Carbolic acid is then added to the broth culture in the proportion of 0.5 per cent, the sediment formed allowed to settle and the supernatant fluid passed through a Berkefeld filter. A good toxin should give, in a dilution of 1:1000 strong positive as well as negative reactions when tested in a group of young children.

The diluted scarlet fever toxin is more stable than the diluted diphtheria toxin used in the Schick test. It can therefore be distributed ready for use. A definite standard has not yet been established for the scarlatinal toxin. It cannot be standardized in animals as it has very little effect on rabbits and practically no effect, even in the undiluted form, on guinea pigs and mice. The following method of standardizing a toxin will be found suitable until a better one is developed. The toxin is standardized by finding a dilution which gives negative reactions in convalescent cases of scarlet fever and good positive (++) reactions in young and susceptible children. It should be emphasized that with a sufficiently low dilution of a toxin, a positive reaction can be brought out in every patient convalescent from scarlet fever. Having established the strength of a standard toxin, it becomes an easy matter to compare by intradermal tests in the same susceptible individual the strength of a newly prepared toxin with that of the standard.

A control test with diluted toxin which has been heated in a waterbath at boiling temperature for an hour should be made at the same time that the test is carried out. The control enables us to differentiate with a fair degree of accuracy the four different reactions already well known in connection with the Schick test: the positive, the negative, the negative-pseudo and the positive-combined reactions.

The *positive* Dick reaction appears more rapidly than the positive Schick reaction. Within 8 to 12 hours one can tell by the result of the test who is susceptible and who is immune to scarlet fever. At the end of 18 to 24 hours the positive Dick reaction resembles closely the positive Schick reaction which has reached its maximum intensity on the fourth day. The Dick reaction, however, fades much more rapidly, only the more strongly positive reactions showing a slight brownish pigmentation at the end of 7 to 10 days. Desquamation is rare, and if

present is very slight. The positive reactions are read as strongly positive (++) when there is a marked redness and local induration; positive (+) when there is local redness with little or no induration; moderately positive (±) or slightly positive (∓) depending on the size and degree of redness in the reaction.

The *negative* reaction shows no change at the site of the test or control.

The *negative-pseudo* reaction shows the same appearance in the test and control. These reactions are due to a protein hypersensitiveness to the autolyzed substance of the hemolytic streptococcus and to the other proteins contained in the test fluid.

The *positive-combined* reaction represents a combination of the positive and negative-pseudo reactions. The reaction in the test with the unheated toxin is usually more pronounced than in the control with the heated toxin.

The positive and positive-combined reactors are susceptible to scarlet fever as far as not having antitoxin is concerned. The negative and negative-pseudo reactors have antitoxin in their blood and are immune to the toxic effects of the scarlatinal streptococcus.

The presence of antitoxin in blood serum (human or horse) can be shown in one of two ways: (1) The serum added to a toxin dilution double the strength used for the Dick test will neutralize the action of the toxin so that no reaction will be produced when the mixture is injected intradermally into a susceptible person; (2) the serum injected in a dose of 1.0 c.c. intradermally into the rash of an early case of scarlet fever will blanch the rash out over an area the size of a twenty-five cent piece to that of a silver dollar (Schultz-Charlton phenomenon).

RESULTS WITH THE DICK TEST IN NORMAL PERSONS

Table 1 shows the results with the Dick test in 7700 persons of different ages. The percentages closely resemble those noted with the Schick test in the same groups. These tests were made in public schools, institutions and hospitals.

TABLE 1

THE DICK TEST AT DIFFERENT AGE GROUPS

Age	Total Tested	Dick Positive	Dick Negative	Per Cent Dick Positive
0–6 months....	29	13	16	44.8
6–12 months..	52	34	18	65.3
1–2 years.....	233	167	66	71.6
2–3 years.....	204	131	73	64.2
3–4 years.....	241	146	95	60.5
4–5 years.....	264	128	136	48.4
5–10 years....	1955	678	1277	33.6
10–15 years....	2965	677	2288	22.8
15–20 years....	981	166	815	16.8
20 years up....	776	112	664	14.4
Total.....	7700	2252	5448	29.2

In two private schools, attended by children of the well-to-do classes of the city's population, we found that 83 per cent of 320 children were susceptible to scarlet fever. A similar high susceptibility to diphtheria we had previously found with the Schick test [17] in the same class of children. Nurses in training schools and students at Teachers College, Columbia University, gave from 40 to 70 per cent positive Dick as well as positive Schick reactions. Many of these individuals came from smaller communities, where they had had but little exposure to infection with the organisms of scarlet fever and diphtheria.

The antitoxic immunity to scarlet fever is transmitted from mother to offspring through the placenta just as it is transmitted in the case of diphtheria. At birth infants show slightly positive or negative reactions when their mothers give respectively positive or negative reactions. The antitoxic immunity persists in those infants for five to six months and is then gradually lost, a large proportion of the children becoming susceptible to scarlet fever at the end of the first year of life.

Several groups of children and adults were tested with both the Dick and Schick tests. The results indicate that two-thirds of the tested gave positive reactions to both tests or negative reactions to both. In groups where the posi-

TABLE 2. SUMMARY OF RESULTS WITH DICK TEST IN ACUTE AND CONVALESCENT CASES OF SCARLET FEVER.

1. Results of First Dick Test on Scarlet Fever Patients at the Time of Admission to Hospital.

Number days of illness before Dick test.	Reaction ++	+	±	∓	—	Number Tested	Total Number Dick Positive	Per Cent Dick Positive
1–5	10	83	97	7	4	201	197	98.0
6 days and over	0	0	9	7	64	80	16	20.0

2. Patients Receiving Dick Test During Acute Stage and During Convalescence from Scarlet Fever.

a)	Total number tested	232
b)	Total number Dick positive on admission to hospital and Dick **negative** during convalescence	213
c)	Total number Dick positive on admission to hospital and Dick **positive** during convalescence	19
d)	Per cent giving negative Dick reaction during convalescence from scarlet fever.	91.3

3. The Dick Test and Schultz-Charlton Phenomenon in Scarlet Fever.

Test	Days of Illness. 1-4 days	5-7 days	8-10 days	11-15 days
Dick test....	+ or ±	±, or ∓ or —	∓ or —	—
Schultz-Charlton..	—	— or ±	± or +	+

tive Dick reactions predominated, a large proportion was found to be positive to the two tests, and where the negative Dick reactions predominated the reverse was found to be the case. The other third of the tested who had different reactions was about evenly divided into two groups: (a) those who gave a positive Dick and a negative Schick reaction, and (b) those who showed a negative Dick and a positive Schick reaction.

RESULT WITH THE DICK TEST IN SCARLET FEVER

Table 2 gives a summary of the results obtained with the Dick test during the past six months among the scarlet fever patients admitted to the Willard Parker Hospital. It will be seen that of 201 patients who were tested during the first five days of illness 197, or 99 per cent, gave positive reactions. These reactions were in the majority of cases + or ±. Strongly positive reactions (++), as seen in normal persons, are not as a rule observed in scarlet fever cases. In most cases some antitoxin has already developed by the second or third day of rash, at a time when many of the cases are usually admitted to the hospital. Of 80 patients tested on admission with a history of six days or more of illness, 64, or 80 per cent, gave negative or negative-pseudo reactions.

Of 232 patients who were tested on admission and also during convalescence 213, or 91.3 per cent, showed a positive reaction on admission and a negative reaction during convalescence. Of the 19 patients who gave a positive reaction during convalescence also, two evidently had had no scarlet fever on admission to the hospital, as they developed the disease five days later and subsequently showed a negative Dick test. Twelve of the remaining 17 patients did not desquamate. It was interesting to note that though 6 of these 12 continued to show a strong positive (++) reaction, indicating that they probably did not have scarlet fever on admission, yet none developed a scarlatinal rash during their stay in the hospital. These patients, although susceptible to the toxin, were probably protected by a local tissue resistance of the nasopharyngeal mucous membrane, which prevents the invasion and toxic action of infectious organisms even in the absence of a general antibody immunity. This local defense mechanism, however, can probably be destroyed by an inflammatory process, such as a cold, or by an operative procedure, such as removal of the tonsils and adenoids.

Five of the patients who continued to show a moderately positive reaction during convalescence desquamated. In two

the desquamation was not characteristic. In one of these two patients it was patchy, confined to parts of arms, shoulders and chest, and left behind it eczema-like areas of skin; in the other slight desquamation was noted on one hand only.

The important question arises whether we are dealing in scarlet fever with one or several different toxins produced by the different agglutinative strains of the specific hemolytic streptococcus. The negative Dick reactions in most of the convalescents from scarlet fever point at least to a great majority as producing a single toxin, such as we know in diphtheria and tetanus. The few positive reactions during convalescence were noted in cases in most of which there can be serious doubt as to the correct diagnosis of scarlet fever. The few patients who desquamated and yet gave a positive Dick reaction during convalescence leave two possibilities open: Either the amount of antitoxin produced during the course of the disease was not sufficient to neutralize the action of the toxin in the Dick test, or there may be occasional strains of hemolytic streptococcus causing scarlet fever that make different toxins, as in the case of *Bacillus botulinus,* which produces two different soluble toxins.

The third part of Table 2 shows that the Dick reaction becomes negative from the sixth to the tenth day of illness. This corresponds with the appearance of antitoxic antibodies in the patient's blood. With the presence of antitoxin the serum acquires the property of blanching the rash (Schultz-Charlton phenomenon) in an early case of scarlet fever. This is indicated in the table by the plus signs. It was significant to note that the Dick reaction became negative a little earlier in convalescence, showing that it requires a certain concentration of antitoxin before the patient's serum can blanch the rash. The Schultz-Charlton test is a rather crude method for the quantitative determination of antitoxin in blood serum as it requires not only a definite concentration to produce a permanent blanching, but many scarlatinal rashes are unsuitable for this test. It is of value, however, as a diagnostic measure to be carried out with a known antitoxic serum in a doubtful case of scarlet fever. Suspicious rashes, especially if well pronounced but not characteristic, could be thus accurately diagnosed. The fine pinpoint rashes do not show the blanching well.

An interesting and significant appearance was noted at the site of the original Dick test in two patients who developed scarlet fever one week after the test. The area on the forearm corresponding to the previous reaction was very pale and surrounded by a sharply defined ring of the scarlet fever rash which was greatly intensified in redness when compared with the rest of the eruption on the forearm. During the height of the eruption a second Dick test was made over the pale area and another one a little to one side. The reaction which developed within the pale area was very slight when compared with the second reaction alongside of it. Apparently a certain amount of cellular immunity had developed at the site of the original positive Dick test. This gave rise to the appearance of the local pallor, which presented such a striking contrast to the rest of the blushed skin and also prevented the development of a good positive reaction during the first day of the disease. The ring of intensified rash making up the border which surrounded the pale area was probably due to the interaction between cells which were sensitized rather than protected by the minute antibody content within their substance and the scarlet fever toxin of the disease. These observations point to the probable local origin in the epidermis of some antitoxin production against scarlet fever.

IMMUNITY RESULTS WITH SCARLET FEVER TOXIN

A convenient method for determining the amount of toxin for active immunization is the skin test dose. The dilution to be used for this purpose depends on the strength of the toxin. If it is used for the Dick test in a dilution of 1:1000, then

1 c.c. of a 1:100 dilution represents 100 skin test doses, the initial dose for active immunization. The second dose is 250 and the third dose 250 skin test doses for children under 3 years. For children over 3 years and up to 12 years the third dose is gradually increased to 500 skin test doses. For adults the third dose may be increased to 1000 skin test doses. In making the dilutions for injecting larger numbers we add 1 c.c., 2.5 c.c. or 5 c.c. of undiluted toxin to 100 c.c. bottles of salt solution, or one-half these amounts to 50 c.c. bottles of salt solution. Where only a few doses are to be administered it is most convenient to make a dilution of the toxin 1:20 which represents 500 skin test doses per c.c. Depending on the age of the person, 0.2 c.c., 0.5 c.c. and 0.5 or 1.0 c.c. would represent the corresponding three doses with this toxin dilution. The injections are given intramuscularly or subcutaneously 7 to 10 days apart.

Local reactions such as slight to moderate redness, induration and tenderness follow as a rule, although they are more frequently seen in older children and adults. The local reactions resemble in degree those noted after the use of 1/10 L + mixtures of diphtheria toxin-antitoxin.

Constitutional reactions are occasionally seen but they are rather infrequent if the initial dose as recommended is a small one and the amount of toxin is gradually increased. The symptoms develop after 12 to 24 hours and consist of varying degrees of temperature, a slight sore throat and occasionally a scarlatiniform rash, that may persist for 24 to 48 hours.

In one adult the rash was followed by desquamation of the palms of the hands. Of more than 2000 children and adults injected with the toxin only 10 had constitutional symptoms associated with a rash, and of these 6 were children under one year of age who had received 100 skin test doses as the initial injection.

These constitutional reactions are not serious, being seen only in persons who are unusually susceptible to the effects of the toxin, yet it would seem desirable to avoid them. For this purpose the toxin can be purified according to the method of Huntoon,[18] which consists in precipitating the toxin with 20 per cent sodium chloride and 1 per cent acetic acid. It is then treated with formaldehyde according to the method suggested by Ramon[19] and by Glenny and Hopkins[20] for diphtheria toxin. This consists in adding 0.1 per cent formaldehyde (0.25 per cent commercial formalin) to a toxin containing from 2 to 5 mgm. amino-nitrogen per 10 c.c., as determined by the van Slyke method, and allowing the toxin to remain at incubator temperature for 4 to 5 weeks. In this way the attempt is made to obtain a modified toxin or toxoid, that will retain its immunizing value and can be used in larger doses without producing constitutional symptoms.

We have found that scarlet fever toxin is neutralized in multiple proportions by

TABLE 3. IMMUNITY RESULTS WITH SCARLET FEVER TOXIN.

DOSES GIVEN: Under 12 Years. 100, 250 and 250 skin test doses at weekly intervals.
Over 12 Years. 100, 250 and 500 skin test doses at weekly intervals.
DICK RETEST AFTER 4-5 WEEKS.

Institutions	Per Cent Positive Dick at Original Test	Dick Positive and Combined.				Dick Negative and Pseudo.	
		Total Retested	Number Positive as in Original Test	Number Less Strongly Positive	Per Cent Less Strongly Positive	Number	Per Cent
Hebrew Orphan Asylum	29.2	143	19	20	14.0	104	72.7
New York Orphanage	44.4	91	10	36	39.5	45	49.4
Leake and Watts Home	22.0	40	12	10	25.0	18	45.0
Total		274	41	66	24.0	167	61.0

the antitoxin. Mixtures of toxin-antitoxin could, therefore, also be prepared similar to the ones used for diphtheria immunization.

Table 3 shows the results with the Dick retest among the children of three institutions, who were injected with the scarlet fever toxin. The retests were made 4 to 5 weeks after the immunizing injections. Sixty-one per cent of the retested children gave negative reactions, and of these a large majority showed negative-pseudo reactions. An additional 24 per cent gave reactions that were less strongly positive than in the original test. The immunity results obtained after the injection of toxin became difficult of interpretation on account of the numerous pseudo-reactions noted in the retest. This can be avoided to a certain extent by using the purified toxin for the Dick test.

ACTIVE IMMUNIZATION OF YOUNG CHILDREN

During the past summer we have injected about 2000 children under the age of 6 years in the Baby Health Stations of Manhattan and the Bronx. These children were injected without a preliminary Dick or Schick test against scarlet fever and diphtheria. The results will be noted by following the cases of scarlet fever and diphtheria developing during the coming year and checking them up against an alphabetical card index list of the injected children.

Each child received 3 doses of scarlet fever toxin and 3 doses of a 1/10 L + mixture of diphtheria toxin-antitoxin, one arm being used for the scarlet fever, the other one for the diphtheria inoculations. It is important to note that the local reactions in these young children are as a rule quite mild. If parents realized this fact thoroughly they would be willing to have their children immunized against these two diseases before they enter school.

SCARLET FEVER ANTITOXIN

Dochez, as well as the Dicks, has described the successful production of an antitoxic serum in horses. Such sera are being prepared at the present time by a number of biological laboratories, including our own, and a concentrated serum will probably be available within a few months. The antitoxin can be used for prophylaxis and treatment along the lines so successfully carried out with diphtheria antitoxin. The dose recommended for purposes of passive immunization is 10 c.c. and for treatment from 20 to 50 c.c. The serum injections are best given intramuscularly.

Where animal antitoxic sera are not available good results will be obtained with the serum or citrated whole blood from convalescents as well as from negative Dick reactors. In testing quantitatively normal individuals by the intracutaneous test with increasing concentrations of scarlet fever toxin I found that some of them show even larger amounts of antitoxin than convalescents.

The effect of antitoxic serum in the treatment of scarlet fever is best seen in the more severe toxic cases that have no septic complications, such as sloughing fauces and enlarged cervical glands. There is a rapid, almost critical drop in temperature, an improvement in the character of the pulse and respiration and more rapid fading of the rash. The improvement in the clinical picture of toxic cases I described a number of years ago[21] after the use of intramuscular injections of citrated convalescent and also of normal blood. There is a similar improvement after the injection of antitoxic horse serum.

SUMMARY AND CONCLUSIONS

1. The Dick test is a reliable method for determining susceptibility and immunity to scarlet fever. In our experience with the test in over 7700 cases, up to the present time 8 positive reactors and none of the negative reactors have developed scarlet fever.

2. The Dick test helps in the diagnosis of doubtful cases of scarlet fever. A strongly positive (++) reaction early in

the disease and again later in convalescence speaks against the diagnosis of scarlet fever. A definite negative reaction during the first two days of rash should also put one on guard that he may not be dealing with scarlet fever.

3. Active immunization with scarlet fever toxin is a safe procedure and is not to any extent associated with the development of constitutional symptoms if the dose of toxin is gradually increased. The skin test is a convenient method for measuring the amount of toxin. Three doses are given at intervals of 7 to 10 days. For children under 3 years, the doses are 100, 250 and 250 skin test doses; over 3 years and up to 12 years the third dose is gradually increased to 500 skin test doses. For adults the third dose may be increased to 1000 skin test doses. A large proportion of the successfully injected individuals show a negative or a negative-pseudo reaction at the retest.

4. Purification of the toxin by the sodium chloride and acetic acid precipitation method gives a preparation that is better for the Dick test and for active immunization, because of lesser protein reactions.

5. The use of toxin treated with formaldehyde to make it practically nontoxic and of toxin-antitoxin mixtures represent further steps in the development of active immunization against scarlet fever.

6. The Dick test applied to 232 cases of scarlet fever showed that 91.3 per cent gave positive reactions during the early stages of the disease and negative reactions during convalescence. There were 19 patients who gave a persistent positive reaction; of these 2 developed scarlet fever subsequently. Of the remaining 17 patients 12 did not desquamate.

7. It is probable that most of the strains of the scarlatinal streptococcus produce a single toxin. The few cases that show positive Dick reactions in convalescence and yet desquamate point either to an insufficient amount of antitoxin in the patient's blood and tissues to neutralize the action of the toxin in the Dick test or to the production of more than one toxin by a few exceptional strains of the scarlatinal streptococcus.

8. The scarlet fever toxin is neutralized in multiple proportions by the antitoxin.

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